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Prevalence of Antimicrobial-Resistant Pathogens in Canadian Hospitals: Results of the Canadian Ward Surveillance Study (CANWARD 2008)[▽]

George G. Zhanel,[1,2,3]* Melanie DeCorby,[1,3] Heather Adam,[1,3] Michael R. Mulvey,[1,6] Melissa McCracken,[6] Philippe Lagacé-Wiens,[1,4] Kimberly A. Nichol,[3] Aleksandra Wierzbowski,[1,3] Patricia J. Baudry,[1,3] Franil Tailor,[1,3] James A. Karlowsky,[1,3] Andrew Walkty,[1,2,3] Frank Schweizer,[1,5] Jack Johnson,[7] the Canadian Antimicrobial Resistance Alliance, and Daryl J. Hoban[1,3]

Department of Medical Microbiology, Faculty of Medicine,[1] Departments of Medicine[2] and Clinical Microbiology,[3] Health Sciences Centre, Department of Clinical Microbiology, St. Boniface General Hospital,[4] and Department of Chemistry, Faculty of Science,[5] University of Manitoba, and Nosocomial Infections Branch, National Microbiology Laboratory,[6] Winnipeg, Manitoba, Canada, and International Health Management Associates, Chicago, Illinois[7]

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A total of 5,282 bacterial isolates obtained between 1 January and 31 December 31 2008, inclusive, from patients in 10 hospitals across Canada as part of the Canadian Ward Surveillance Study (CANWARD 2008) underwent susceptibility testing. The 10 most common organisms, representing 78.8% of all clinical specimens, were as follows: *Escherichia coli* (21.4%), methicillin-susceptible *Staphylococcus aureus* (MSSA; 13.9%), *Streptococcus pneumoniae* (10.3%), *Pseudomonas aeruginosa* (7.1%), *Klebsiella pneumoniae* (6.0%), coagulase-negative staphylococci/*Staphylococcus epidermidis* (5.4%), methicillin-resistant *S. aureus* (MRSA; 5.1%), *Haemophilus influenzae* (4.1%), *Enterococcus* spp. (3.3%), *Enterobacter cloacae* (2.2%). MRSA comprised 27.0% (272/1,007) of all *S. aureus* isolates (genotypically, 68.8% of MRSA were health care associated [HA-MRSA] and 27.6% were community associated [CA-MRSA]). Extended-spectrum β-lactamase (ESBL)-producing *E. coli* occurred in 4.9% of *E. coli* isolates. The CTX-M type was the predominant ESBL, with CTX-M-15 the most prevalent genotype. MRSA demonstrated no resistance to ceftobiprole, daptomycin, linezolid, telavancin, tigecycline, or vancomycin (0.4% intermediate intermediate resistance). *E. coli* demonstrated no resistance to ertapenem, meropenem, or tigecycline. Resistance rates with *P. aeruginosa* were as follows: colistin (polymyxin E), 0.8%; amikacin, 3.5%; cefepime, 7.2%; gentamicin, 12.3%; fluoroquinolones, 19.0 to 24.1%; meropenem, 5.6%; piperacillin-tazobactam, 8.0%. A multidrug-resistant (MDR) phenotype occurred frequently in *P. aeruginosa* (5.9%) but uncommonly in *E. coli* (1.2%) and *K. pneumoniae* (0.9%). In conclusion, *E. coli*, *S. aureus* (MSSA and MRSA), *P. aeruginosa*, *S. pneumoniae*, *K. pneumoniae*, *H. influenzae*, and *Enterococcus* spp. are the most common isolates recovered from clinical specimens in Canadian hospitals. The prevalence of MRSA was 27.0% (of which genotypically 27.6% were CA-MRSA), while ESBL-producing *E. coli* occurred in 4.9% of isolates. An MDR phenotype was common in *P. aeruginosa*.

The prevalence of antimicrobial-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA; either community associated [CA-MRSA] or health care associated [HA-MRSA]), vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* species, and fluoroquinolone-resistant and carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*, is increasing in all regions of Canada, the United States, and globally (2, 3, 5, 6, 12, 19, 21, 24, 26, 27, 28, 30, 35, 37, 38). These organisms commonly display a multidrug-resistant (MDR) phenotype (concomitant resistance to ≥3 different antimicrobial classes), further limiting treatment options (2, 3, 19, 21, 24, 35, 37–39).

The purpose of the Canadian Ward Surveillance Study (CANWARD) study was to assess the prevalence of pathogens, including the resistance genotypes of MRSA, VRE, and ESBL isolates, causing infections in Canadian hospitals as well as their antimicrobial resistance patterns. The CANWARD study is the first ongoing, national, prospective surveillance study assessing antimicrobial resistance in Canadian hospitals. The results of CANWARD 2007 were previously published (39), and the data are available on the official website of the Canadian Antimicrobial Resistance Alliance (CARA; www.can-r.ca).

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MATERIALS AND METHODS

Bacterial isolates. The CANWARD 2008 study included 10 medical centers from all regions of Canada (see Acknowledgments and www.can-r.ca). From 1 January to 31 December 2008, inclusive, each center collected and submitted clinical isolates from patients attending hospital clinics, emergency rooms (ER), medical and surgical wards, and intensive care units (ICUs). Each center was asked to submit clinically significant isolates (unique, consecutive; 1 organism/infection site per patient) from blood (240 isolates

* Corresponding author. Mailing address: Clinical Microbiology, Health Sciences Centre, MS673, 820 Sherbrook St., Winnipeg, Manitoba R3A 1R9, Canada. Phone: (204) 787-4902. Fax: (204) 787-4699. E-mail: ggzhanel@pcs.mb.ca.

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collected [20 consecutive samples/month for each of the 12 months]), respiratory (150), urine (100), and wound (50) infections. Criteria for exclusion were the following: surveillance swabs; eye, ear, nose and throat swabs; duplicate swabs (i.e., not unique isolates); polymicrobial cultures. Additionally, anaerobic organisms and fungal organisms, except *Candida* species from blood cultures, were excluded. All organisms were identified and deemed clinically significant at the originating center based on local site criteria. In CANWARD 2008, 5,282 isolates were collected from 4,260 patients (1.24 isolates/patient). Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) on Amies charcoal swabs, subcultured onto appropriate media, and stocked in skim milk at −80°C until MIC testing was carried out.

Antimicrobial susceptibility testing. Following two subcultures from frozen stock, the *in vitro* activities of amikacin, amoxicillin-clavulanate, cefazolin, ceftazidime, ceftriaxone, cefepime, ceftobiprole, ciprofloxacin, clarithromycin, clindamycin, colistin (polymyxin E), daptomycin, doripenem, ertapenem, gentamicin, levofloxacin, linezolid, meropenem, moxifloxacin, nitrofurantoin, piperacillin-tazobactam, telavancin, tigecycline, trimethoprim-sulfamethoxazole (SXT), and vancomycin were determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (9). Susceptibility testing was not performed for all antimicrobial agents due to a lack of space on the susceptibility panels. The MICs were determined using 96-well custom-designed broth microtiter panels, which were made in-house with antimicrobial agents obtained as laboratory-grade powders from their respective manufacturers, and stock solutions were prepared and dilutions made as described by CLSI (9). The microtiter panels were inoculated to achieve a final concentration of approximately 5×10^5 CFU/ml and incubated in ambient air prior to reading. Colony counts were performed periodically to confirm that the appropriate inocula were used. Quality control (QC) was performed using ATCC QC organisms *S. pneumoniae* 49619, *S. aureus* 29213, *Enterobacter faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

CLSI breakpoints were used for all antimicrobial agent-organism combinations for which interpretative criteria were available (10). For agents without CLSI interpretative criteria, FDA and Health Canada breakpoints were applied. The following FDA breakpoints (susceptible [S], intermediate [I], and resistant [R]) were used for tigecycline: *S. aureus* (methicillin susceptible [MSSA] and MRSA), ≤0.5 μg/ml (S); *E. faecalis* (vancomycin susceptible), ≤0.25 μg/ml (S); *Enterobacteriaceae*, ≤2 μg/ml (S), 4 μg/ml (I), and ≥8 μg/ml (R). The following Health Canada interpretive breakpoints were used for ceftobiprole, which is commercially available in Canada: *S. aureus* (MSSA and MRSA), ≤4.0 μg/ml (S); *Enterobacteriaceae*, ≤1 μg/ml (S), 2 μg/ml (I), and ≥4 μg/ml (R). The following FDA breakpoint for telavancin and *S. aureus* (MSSA and MRSA) was used: ≤1 μg/ml (S).

Characterization of MRSA, ESBL-producing *E. coli*, and VRE. (i) MRSA. Potential MRSA isolates were confirmed using the CLSI disk diffusion method with cefoxitin and by multiplex PCR of the *mecA* and *nuc* genes. All MRSA isolates were tested by PCR for the Panton-Valentine leukocidin gene (*pvl*). Additionally, all MRSA isolates were typed using pulsed-field gel electrophoresis (PFGE) and spa typing following the Canadian standardized protocol to assess whether the isolates were community associated or health care associated (8, 15, 23–25). PFGE fingerprints were analyzed with BioNumerics version 3.5 (Applied Maths, Austin, TX), and strain relatedness was determined as previously described (33). The PFGE fingerprints were compared to the national MRSA fingerprint database and were grouped into 1 of 10 Canadian epidemic MRSA strain types (CMRSA-1 to CMRSA-10) as previously described (23). In the CANWARD study, CA-MRSA and HA-MRSA were defined genotypically; MRSA isolates with a CMRSA-7 (USA400/MW2) or CMRSA-10 (USA300) genotype were labeled as CA-MRSA, while all other genotypes (e.g., CMRSA-1 [USA600], CMRSA-2 [USA100], CMRSA-4 [USA200], etc.) were labeled as HA-MRSA (23, 24, 38).

(ii) ESBL. Any *E. coli* or *Klebsiella* spp. with a ceftriaxone and/or ceftazidime MIC of ≥1 μg/ml was identified as a potential ESBL producer as specified by CLSI (10, 22). The potential ESBL-producing organisms were phenotypically confirmed using the CLSI confirmatory method (10). PCR and DNA sequence analysis were used to identify bla_{SHV}, bla_{TEM}, and $bla_{CTX\text{-}M}$ genes among all ESBL-producing *E. coli* and *Klebsiella* species isolates, as previously described (2, 3, 27).

(iii) VRE. Potential VRE isolates were confirmed using CLSI vancomycin disk diffusion testing and underwent *vanA* and *vanB* PCR as well as PFGE typing to assess genetic similarity, as previously described (12, 36).

Statistical analyses. To analyze factors associated with antimicrobial resistance, all organisms were classified by the number of antimicrobial classes (0 to ≥5) to which they displayed resistance, regardless of species. Only antimicrobial-organism combinations for which CLSI interpretative criteria exist were considered in this analysis. Univariate χ^2 analysis was used to evaluate statistically significant associations between the number of antimicrobial classes to which resistance was observed and gender, age, geographic region, inpatient status, and invasive (blood culture) isolates. Factors found to have a P value of <0.10 in the univariate analysis were included in a full factorial ordinal logistic regression model to determine the variables that were independently associated with resistance. Finally, a separate nominal logistic regression model using multidrug resistance (≥3 classes) in Gram-negative organisms and pan-susceptibility (susceptibility to all antimicrobial classes tested) in all organisms as the response variables was also considered. All statistical analyses were done using JMP 8.0 software (SAS Institute, Cary, NC).

RESULTS

Patient demographics and specimen types. A total of 5,282 isolates recovered from clinical specimens were collected from hospitals across Canada as part of CANWARD 2008. Overall, 53.7% (2,838/5,282) of the isolates were collected from males. The patient age breakdown was as follows: ≤17 years, 14.4% (760/5,282); 18 to 64 years, 44.9% (2,370/5,282); ≥65 years, 40.7% (2,152/5,282). With regard to specimen source, 30.5% (1,612/5,282) of the organisms were obtained from respiratory specimens, 41.5% (2,194/5,282) from blood, 9.3% (493/5,282) from wounds, and 18.6% (983/5,282) from urine.

Predominant organisms isolated in Canadian hospitals. The 20 most commonly isolated organisms in hospitals across Canada are listed in Table 1. For Gram-positive cocci, *S. aureus* (MSSA), *S. pneumoniae*, MRSA, *Enterococcus* spp., and coagulase-negative staphylococci(CNS)/*Staphylococcus epidermidis* collectively represented 38.0% of all isolates. For Gram-negative bacilli, *E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Enterobacter cloacae* represented 40.8% of all organisms.

Predominant organisms isolated by specimen site. Table 2 describes the 10 most commonly isolated microorganisms recovered from the four evaluated specimen sources (respiratory, blood, wounds, and urine). *S. pneumoniae*, *S. aureus* (MSSA), and *P. aeruginosa* were the most commonly isolated pathogens from respiratory tract specimens (>50% of isolates). Among blood culture isolates, *E. coli*, *S. aureus* (MSSA), and coagulase-negative staphylococci/*S. epidermidis* were the most predominant. *S. aureus* (MSSA and MRSA) was the most commonly isolated organism from wound cultures (~50% of wound pathogens). Among urinary tract specimens, *E. coli* was the predominant pathogen (51.9%), while enterococci (14.5%) and *K. pneumoniae* (10%) were also frequently identified.

Characteristics of MRSA. Twenty-seven percent (272/1,007) of all *S. aureus* isolates were MRSA. The prevalence of MRSA varied geographically: British Columbia/Alberta, 31.6%; Quebec/Maritimes, 30.9%; Ontario, 25.7%; Manitoba/Saskatchewan, 19.3%. Genotypically (as determined by PFGE), 68.8% of MRSA were HA-MRSA and 27.6% were CA-MRSA (3.8% of MRSA could not be genotypically classified). CMRSA-10/USA300 represented 80.0%, whereas 20.0% of the CA-MRSA were CMRSA-7/USA400. PFGE patterns among HA-MRSA included CMRSA-2/USA100/

TABLE 1. The 20 most common organisms isolated from Canadian hospitals

Ranking	Organism	No. of isolates	% of total
1	*Escherichia coli*	1,132	21.4
2	*Staphylococcus aureus* MSSA	735	13.9
3	*Streptococcus pneumoniae*	544	10.3
4	*Pseudomonas aeruginosa*	373	7.1
5	*Klebsiella pneumoniae*	316	6.0
6	CNS/*S. epidermidis*	283	5.4
7	*Staphylococcus aureus* MRSA	272	5.1
8	*Haemophilus influenzae*	214	4.1
9	*Enterococcus* spp.	176	3.3
10	*Enterobacter cloacae*	114	2.2
11	*Enterococcus faecalis*	101	1.9
12	*Streptococcus pyogenes*	97	1.8
13	*Proteus mirabilis*	85	1.6
14	*Klebsiella oxytoca*	76	1.4
15	*Streptococcus agalactiae*	73	1.4
16	*Serratia marcescens*	69	1.3
17	*Stenotrophomonas maltophilia*	57	1.1
18	*Moraxella catarrhalis*	52	1.0
19	*Enterococcus faecium*	49	0.9
20	*Viridans group Streptococci*	44	0.8
	Other[a]	420	8.0
Total		5,282	100.0

[a] Other organisms included the following: *Acinetobacter* spp., *Aeromonas* spp., *Alcaligenes* spp., *Bacillus* spp., *Brevibacterium* spp., *Candida* spp., *Cedecea* spp., *Chryseobacterium* spp., *Citrobacter* spp., *Corynebacterium* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Gemella* spp., *Granulicatella* spp., *Haemophilus* spp., *Hafnia* spp., *Klebsiella* spp., *Listeria* spp., *Micrococcus* spp., *Moraxella* spp., *Morganella* spp., *Neisseria* spp., *Pantoea* spp., *Pasteurella* spp., *Proteus* spp., *Providencia* spp., *Pseudomonas* spp., *Ralstonia* spp., *Salmonella* spp., *Serratia* spp., *Staphylococcus* spp., and *Streptococcus* spp.

800 (81.9%), CMRSA-3 or CMRSA-6 (12.8%), CMRSA-1/USA600 (1.6%), CMRSA-5/USA500 (1.6%), CMRSA-8 (1.1%), CMRSA-4/USA200 (0.5%), and CMRSA-9 (0.5%). PVL was detected in 85.3% of CA-MRSA and 0.5% of HA-MRSA isolates.

Characteristics of ESBL-producing *E. coli* and *K. pneumoniae*. Of the *E. coli* isolates tested, 4.9% (55/1,132) were ESBL producing. The proportion of *E. coli* isolates producing ESBLs varied by medical unit: 2.5% in hospital clinics, 2.9% in surgical wards, 4.6% in emergency rooms, 5.9% in medical wards, and 8.0% in intensive care units. The prevalence of ESBL-producing *E. coli* isolates varied geographically: British Columbia/Alberta, 7.6%; Ontario, 5.8%; Manitoba/Saskatchewan, 4.7%; Quebec/Maritimes, 2.4%. Of the 55 ESBL-producing *E. coli*, 49 (89.1%) carried ESBL genes from the CTX-M group (39 [70.9%] $bla_{\text{CTX-M-15}}$, 8 [14.5%] $bla_{\text{CTX-M-14}}$, and 2 [3.6%] $bla_{\text{CTX-M-27}}$), 2 (3.6%) carried bla_{SHV2a}, 1 (2.2%) carried $bla_{\text{TEM-12}}$, and for 3 (5.5%) the ESBL gene was unknown. An MDR phenotype was observed in 76.4% of the ESBL-producing *E. coli.* ESBL production was detected in 3.2% (10/316) of the *K. pneumoniae* isolates, with Ontario recording 50% (5/10) of all strains. An MDR phenotype was observed in 80.0% of the ESBL-producing *K. pneumoniae.*

TABLE 2. The 10 most common organisms isolated in Canadian hospitals, by specimen site

Site (% of total isolates) and ranking	Organism	No. of isolates	% of total
Respiratory (30.5)			
1	*S. pneumoniae*	423	26.2
2	*S. aureus* MSSA	237	14.7
3	*P. aeruginosa*	217	13.5
4	*H. influenzae*	201	12.5
5	*S. aureus* MRSA	91	5.6
6	*K. pneumoniae*	66	4.1
7	*E. coli*	60	3.7
8	*M. catarrhalis*	52	3.2
9	*S. maltophilia*	42	2.6
10	*S. marcescens*	32	2.0
Other		191	11.9
Total		1,612	100.0
Blood (41.5)			
1	*E. coli*	522	23.8
2	*S. aureu* MSSA	299	13.6
3	CNS /*S. epidermidis*	256	11.7
4	*K. pneumoniae*	139	6.3
5	*S. pneumoniae*	121	5.5
6	*S. aureus* MRSA	109	5.0
7	*E. faecalis*	94	4.3
8	*P. aeruginosa*	81	3.7
9	*E. cloacae*	48	2.2
10	*S. agalactiae*	45	2.1
Other		480	21.8
Total		2,194	100.0
Wounds (9.3)			
1	*S. aureus* MSSA	184	37.3
2	*S. aureus* MRSA	58	11.8
3	*E. coli*	40	8.1
4	*P. aeruginosa*	40	8.1
5	*S. pyogenes*	37	7.5
6	*Enterococcus* spp.	22	4.5
7	*E. cloacae*	14	2.8
8	*K. pneumoniae*	13	2.6
9	CNS/*S. epidermidis*	10	2.0
10	*S. agalactiae*	8	1.6
Other		67	13.7
Total		493	100.0
Urine (18.6)			
1	*E. coli*	510	51.9
2	*Enterococcus* spp.	143	14.5
3	*K. pneumoniae*	98	10.0
4	*P. mirabilis*	46	4.7
5	*P. aeruginosa*	35	3.6
6	*E. cloacae*	22	2.2
7	*K. oxytoca*	17	1.7
8	CNS/*S. epidermidis*	16	1.6
9	*S. aureus* MSSA	15	1.5
10	*S. aureus* MRSA	14	1.4
Other		67	6.9
Total		983	100.0

Characteristics of VRE. Among the 320 enterococci, 10 (3.1%) were VRE. All VRE detected were *E. faecium* and displayed the *vanA* genotype.

Antimicrobial susceptibility testing. Antimicrobial resistance rates for the most common Gram-positive cocci based on specimen source are listed in Table 3. Among MSSA, no resistance was observed to ceftobiprole (MIC_{90}, 0.5 μg/ml

TABLE 3. Resistance rates for the most common Gram-positive cocci isolated from Canadian hospitals, based on specimen source[a]

Organism and source (*n*)	% I/% R													
	CFZ	CPM	CTR	PTZ	ETP	MER	CIP[c]	LEV	MXF	CLR	CD	LZD	TGC	SXT	FD	DAP	VAN
S. aureus																	
MSSA																	
All (735)	0/0	0/0	0/0	0/0	0/0	0/0	3.4/9.2	0.4/8.0	0.7/7.5	0.1/23.5	0.9/6.5	0/0	0/0	0/1.2	0/0	0/0	0/0
Blood (299)	0/0	0/0	0/0	0/0	0/0	0/0	2.3/8.0	0/7.4	0.3/7.0	0/22.4	0/5.0	0/0	0/0	0/0.7	0/0	0/0	0/0
Urine (15)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wound (184)	0/0	0/0	0/0	0/0	0/0	0/0	1.6/7.1	0.5/5.4	1.1/4.3	0/21.2	0.5/7.1	0/0	0/0	0/2.7	0/0	0/0	0/0
Respiratory (237)	0/0	0/0	0/0	0/0	0/0	0/0	6.3/11.0	0.8/9.3	0.8/8.9	0.4/26.6	2.5/6.7	0/0	0/0	0/0.8	0/0	0/0	0/0
MRSA																	
All (272)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/87.1	0/86.4	0/86.4	0.4/85.7	0/55.5	0/0	0/0	0/10.3	0/0	0/0	0.4/0
Blood (109)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/81.6	0/81.6	0/81.6	0.9/83.5	0/51.4	0/0	0/0	0/11.9	0/0	0/0	0.9/0
Urine (14)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wound (58)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/81.0	0/77.6	0/77.6	0/81.0	0/36.2	0/0	0/0	0/5.2	0/0	0/0	0/0
Respiratory (91)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/95.6	0/95.6	0/95.6	0/89.0	0/71.4	0/0	0/0	0/11.0	0/0	0/0	0/0
S. pneumoniae																	
All (544)	–	–	0.6/0.2	–	0/0	3.3/1.7	4.7	0.4/1.2	0.4/1.0	2.1/17.5	0.4/8.2	0/0	–	7.5/10.0	–	–	0/0
Blood (121)	–	–	0/0	–	0/0	0.9/0.9	0.0	0/0	0/0	1.7/12.3	0/7.0	0/0	–	6.8/7.7	–	–	0/0
Urine (NA)	–	–	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	–	NA	–	–	NA
Wound (NA)	–	–	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	–	NA	–	–	NA
Respiratory (423)	–	–	0.7/0.2	–	0/0	4.0/2.0	6.0	0.5/1.5	0.5/1.2	2.2/18.9	0.5/8.5	0/0	–	7.6/10.6	–	–	0/0

[a] I, intermediate; R, resistant; NA, no isolates met criteria or there were insufficient numbers for analysis ($n < 40$); –, no defined breakpoints; CFZ, cefazolin; CPM, cefepime; CTR, ceftriaxone; PTZ, piperacillin-tazobactam; ETP, ertapenem; MER, meropenem; CIP, ciprofloxacin; LEV, levofloxacin; MXF, moxifloxacin; CLR, clarithromycin; CD, clindamycin; LZD, linezolid; TGC, tigecycline; FD, nitrofurantoin; DAP, daptomycin; VAN, vancomycin.

[b] Based on oxacillin susceptibility.

[c] For *S. pneumoniae*, only the percentage of resistant isolates (≥4 μg/ml) for ciprofloxacin is shown.

[data not shown]), daptomycin, linezolid, telavancin (MIC_{90}, 0.5 μg/ml [data not shown]), tigecycline, or vancomycin. The MIC_{90}s (in μg/ml) to dalbavancin and oritavancin were 0.06 and 0.5, respectively (data not shown). Resistance rates with MSSA were as follows: clarithromycin, 23.5%; clindamycin, 6.5%; fluoroquinolones, 7.5 to 9.2%; SXT, 1.2% (Table 3). With MRSA, no resistance was observed with ceftobiprole (MIC_{90}, 2 μg/ml [data not shown]), daptomycin, linezolid, telavancin (MIC_{90}, 0.5 μg/ml [data not shown]), tigecycline, and vancomycin (0.4% intermediate). The MIC_{90}s (in μg/ml) to dalbavancin and oritavancin were 0.06 and 0.5, respectively (data not shown). Resistance rates with MRSA were as follows: clarithromycin, 85.7%; clindamycin, 55.5%; fluoroquinolones, 86.4 to 87.1%; SXT, 10.3% (Table 3). With *S. pneumoniae*, no resistance was observed to vancomycin, linezolid, or ertapenem. The MIC_{90}s (in μg/ml) to dalbavancin, oritavancin, and telavancin were ≤0.03, 0.004, and ≤0.03, respectively (data not shown). Resistance rates with *S. pneumoniae* were as follows: fluoroquinolones, 1.0 to 4.7%; ceftriaxone, 0.2%; meropenem, 1.7%; clarithromycin, 17.5%; clindamycin, 8.2%; SXT, 10.0% (Table 3). Resistance rates for tested antimicrobials were higher in *S. pneumoniae* isolates obtained from respiratory versus blood specimens (Table 3).

Resistance rates for the most common Gram-positive cocci based on hospital ward location are listed in Table 4. *S. aureus* (MSSA and MRSA) resistance rates for fluoroquinolones, clarithromycin, clindamycin, and SXT were not influenced by ward location. With *S. pneumoniae*, resistance rates with fluoroquinolones, clarithromycin, and clindamycin tended to be higher on medical wards than other hospital locations.

For Gram-positive organisms, the ordinal logistic regression model showed increasing age ($P < 0.001$), inpatient status ($P < 0.001$), and invasive isolates ($P < 0.001$) were associated with higher resistance rates. The nominal logistic regression model showed that pan-susceptibility was associated with lower age ($P = 0.003$), outpatient status ($P < 0.001$), and noninvasive isolates ($P < 0.001$).

Antimicrobial resistance rates for the most common Gram-negative bacilli based on specimen source are listed in Table 5. With *E. coli*, no resistance was observed to doripenem, ertapenem, meropenem, and tigecycline. Resistance rates with *E. coli* against other agents were as follows: amoxicillin-clavulanate, 0.5%; cefazolin, 10.0%; cefepime, 1.6%; ceftriaxone, 4.4%; gentamicin, 9.7%; fluoroquinolones, 21.6 to 22.1%; piperacillin-tazobactam, 1.2%; SXT, 27.7%. Resistance rates with *P. aeruginosa* were as follows: amikacin, 3.5%; cefepime, 7.2%; gentamicin, 12.3%; fluoroquinolones, 19.0 to 24.1%; meropenem, 5.6% (meropenem MIC_{90}, 8 μg/ml, versus doripenem MIC_{90}, 4 μg/ml); piperacillin-tazobactam, 8.0%; colistin (polymyxin E), 0.8%. *P. aeruginosa* resistance rates with aminoglycosides, fluoroquinolones, and colistin were higher in isolates obtained from respiratory specimens. With *K. pneumoniae*, no resistance was observed to amoxicillin-clavulanate, doripenem, ertapenem, and meropenem. Resistance rates with *K. pneumoniae* were as follows: cefazolin, 6.3%; ceftriaxone, 1.3%; cefepime, 0.9%; fluoroquinolones, 5.1 to 7.3%; amikacin, 0.6%; gentamicin, 2.8%; piperacillin-tazobactam, 2.5%;

TABLE 4. Resistance rates for the most common Gram-positive cocci isolated from Canadian hospitals, based on hospital location[a]

Organism and location (*n*)	% I/% R																
	CFZ	CPM	CTR	PTZ	ETP	MER	CIP[c]	LEV	MXF	CLR	CD	LZD	TGC	SXT	FD	DAP	VAN
S. aureus																	
MSSA																	
All (735)	0/0	0/0	0/0	0/0	0/0	0/0	3.4/9.2	0.4/8.0	0.7/7.5	0.1/23.5	0.9/6.5	0/0	0/0	0/1.2	0/0	0/0	0/0
Clinic (152)	0/0	0/0	0/0	0/0	0/0	0/0	9.9/7.9	1.3/5.9	0.7/5.9	0/27.0	3.3/7.2	0/0	0/0	0/1.3	0/0	0/0	0/0
ER (211)	0/0	0/0	0/0	0/0	0/0	0/0	1.9/9.0	0/8.5	0.5/8.1	0.5/25.1	0/6.2	0/0	0/0	0/0.9	0/0	0/0	0/0
ICU (105)	0/0	0/0	0/0	0/0	0/0	0/0	0.9/13.3	0/11.4	0/11.4	0/22.9	0/6.7	0/0	0/0	0/1.9	0/0	0/0	0/0
Medical (178)	0/0	0/0	0/0	0/0	0/0	0/0	1.1/8.4	0.6/7.3	0.6/6.7	0/19.7	1.1/6.7	0/0	0/0	0/1.1	0/0	0/0	0/0
Surgical (89)	0/0	0/0	0/0	0/0	0/0	0/0	3.4/9.0	0/7.9	2.2/5.6	0/22.5	0/5.6	0/0	0/0	0/1.1	0/0	0/0	0/0
MRSA																	
All (272)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/87.1	0/86.4	0/86.4	0.4/85.7	0/55.5	0/0	0/0	0/10.3	0/0	0/0	0.4/0
Clinic (24)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ER (69)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/88.4	0/88.4	0/88.4	0/85.5	0/37.7	0/0	0/0	0/2.9	0/0	0/0	1.4/0
ICU (50)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/86.0	0/86.0	0/86.0	2.0/82.0	0/62.0	0/0	0/0	0/22.0	0/0	0/0	0/0
Medical (85)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/88.2	0/88.2	0/88.2	0/87.1	0/67.1	0/0	0/0	0/8.2	0/0	0/0	0/0
Surgical (44)	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/100[b]	0/86.4	0/81.8	0/81.8	0/90.9	0/56.8	0/0	0/0	0/15.9	0/0	0/0	0/0
S. pneumoniae																	
All (544)	–	–	0.6/0.2	–	0/0	3.3/1.7	4.7	0.4/1.2	0.4/1.0	2.1/17.5	0.4/8.2	0/0	–	7.5/10.0	–	–	0/0
Clinic (93)	–	–	0/0	–	0/0	4.7/3.5	5.9	0/1.2	0/1.2	0/16.5	0/7.1	0/0	–	2.3/16.1	–	–	0/0
ER (152)	–	–	0/0	–	0/0	0.7/1.4	2.8	0/0.7	0/0.7	2.1/13.4	1.4/7.0	0/0	–	6.8/4.8	–	–	0/0
ICU (132)	–	–	1.6/0	–	0/0	2.4/0.8	4.0	0/0	2.4/0.8	1.6/16.0	0/7.2	0/0	–	7.9/10.3	–	–	0/0
Medical (129)	–	–	0.8/0.8	–	0/0	5.6/0.8	6.4	1.6/3.2	1.6/2.4	3.2/24.0	0/11.2	0/0	–	8.8/9.6	–	–	0/0
Surgical (38)	–	–	NA	–	NA	NA	NA	NA	NA	NA	NA	NA	–	NA	–	–	NA

[a] I, intermediate; R, resistant; NA, no isolates met criteria or there were insufficient numbers for analysis ($n < 40$); –, no defined breakpoints; CFZ, cefazolin; CPM, cefepime; CTR, ceftriaxone; PTZ, piperacillin-tazobactam; ETP, ertapenem; MER, meropenem; CIP, ciprofloxacin; LEV, levofloxacin; MXF, moxifloxacin; CLR, clarithromycin; CD, clindamycin; LZD, linezolid; TGC, tigecycline; FD, nitrofurantoin; DAP, daptomycin; VAN, vancomycin.

[b] Based on oxacillin susceptibility.

[c] For *S. pneumoniae*, only the percentage of resistant isolates (≥4 μg/ml) for ciprofloxacin is shown.

TABLE 5. Resistance rates for the most common Gram-negative bacilli isolated from Canadian hospitals, based on specimen source[a]

Organism and source (*n*)	% I/% R													
	A/C	CFZ	CPM	CTR	FOX	ETP	MER	PTZ	AMK	GEN	CIP	LEV	MXF	COL	FD[b]	SXT	TGC
E. coli																	
All (1132)	1.4/0.5	2.2/10.0	1.1/1.6	0.9/4.4	3.6/5.6	0/0	0/0	1.9/1.2	0.2/0.3	0.3/9.7	0.2/22.1	0.5/21.6	–	–	1.9/1.1	0/27.7	0.2/0
Blood (522)	1.0/0.2	2.7/9.8	2.1/1.0	1.1/5.0	2.9/4.8	0/0	0/0	2.1/1.0	0.2/0.6	0.2/10.5	0.2/21.6	0.6/21.3	–	–	1.2/0.8	0/31.6	0/0
Urine (510)	1.6/0.6	1.6/9.2	0.4/2.3	0.4/4.1	3.7/6.1	0/0	0/0	1.6/0.8	0/0.2	0.4/8.2	0.2/21.4	0.4/21.0	–	–	2.0/1.6	0/24.3	0.4/0
Wound (40)	0/5.0	2.5/12.5	0/0	5.0/2.5	5.0/15.0	0/0	0/0	2.5/2.5	2.5/0	2.5/7.5	0/22.5	0/22.5	–	–	5.0/0	0/25.0	0/0
Respiratory (60)	5.0/0	3.3/16.7	0/1.7	0/3.3	8.3/3.3	0/0	0/0	3.3/6.7	0/0	0/16.7	0/31.7	1.7/30.0	–	–	0/0	0/25.0	0/0
P. aeruginosa																	
All (373)	–	–	12.1/7.2	45.8/32.7	–	–	4.0/5.6	0/8.0	2.7/3.5	16.6/12.3	5.6/19.0	11.3/24.1	–	7.2/0.8	–	–	–
Blood (81)	–	–	4.9/7.4	50.6/29.6	–	–	1.2/8.6	0/6.2	2.5/1.2	13.6/7.4	1.2/16.0	13.6/16.0	–	7.4/0	–	–	–
Urine (35)	–	–	NA	NA	–	–	NA	NA	NA	NA	NA	NA	–	NA	–	–	–
Wound (40)	–	–	10.0/7.5	42.5/42.5	–	–	2.5/5.0	0/7.5	0/0	15.0/5.0	2.5/20.0	2.5/22.5	–	7.5/0	–	–	–
Respiratory (217)	–	–	16.1/6.9	44.2/30.4	–	–	6.0/4.1	0/8.8	3.2/5.5	18.4/15.7	7.4/18.4	12.9/25.8	–	6.9/1.4	–	–	–
K. pneumoniae																	
All (316)	2.8/0	4.8/6.3	0.3/0.9	1.6/1.3	4.1/3.5	0/0	0/0	1.9/2.5	0/0.6	0.6/2.8	2.2/7.3	1.3/5.1	–	–	31.3/32.6	0/11.4	3.8/0.6
Blood (139)	2.9/0	2.9/5.8	0/0.7	1.4/0.7	2.9/3.6	0/0	0/0	0.7/1.4	0/0	0.7/1.4	2.9/4.3	0.7/2.9	–	–	38.8/26.6	0/11.5	1.4/0.7
Urine (98)	0/0	2.0/7.1	1.0/1.0	1.0/2.0	8.2/1.0	0/0	0/0	4.1/3.1	0/1.0	1.0/5.1	2.0/12.2	2.0/8.2	–	–	21.4/45.9	0/15.3	7.1/0
Wound (13)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA
Respiratory (66)	6.1/0	10.6/6.1	0/1.5	1.5/1.5	0/6.1	0/0	0/0	1.5/4.5	0/1.5	0/1.5	0/4.5	0/3.0	–	–	28.8/22.7	0/4.5	3.0/0

[a] I, intermediate; R, resistant; NA, no isolates met criteria or there were insufficient numbers for analysis ($n < 40$); –, no defined breakpoints; A/C, amoxicillin-clavulanate; CFZ, cefazolin; CPM, cefepime; CTR, ceftriaxone; FOX, cefoxitin; ETP, ertapenem; MER, meropenem; PTZ, piperacillin-tazobactam; AMK, amikacin; GEN, gentamicin; CIP, ciprofloxacin; LEV, levofloxacin; MXF, moxifloxacin; COL, colistin; FD, nitrofurantoin; TGC, tigecycline.

[b] Indicated for use against urinary tract isolates only (CLSI M100-S19).

tigecycline, 0.6%; SXT, 11.4%. *K. pneumoniae* resistance rates with aminoglycosides and fluoroquinolones were higher in isolates from urinary specimens.

Antimicrobial resistance rates for the most common Gram-negative bacilli based on hospital ward location are listed in Table 6. With *E. coli*, antimicrobial resistance rates for penicillins, cephalosporins, fluoroquinolones, and aminoglycosides were highest in isolates obtained from ICUs. With *P. aeruginosa* (excluding the cystic fibrosis clinics), resistance rates were highest in ICU specimens for penicillins, cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides.

The ordinal logistic regression model showed that Gram-negative bacilli were resistant to more classes of antimicrobials when obtained from inpatients ($P < 0.001$) and men ($P < 0.001$). Similarly, Gram-negative isolates were more likely to be pan-susceptible when obtained from outpatients ($P < 0.001$) and women ($P < 0.001$).

MDR. Multidrug resistance was assessed in Gram-negative organisms only, because no accepted definition exists for Gram-positive organisms (Table 7). Multidrug resistance for Gram-negative organisms was defined as resistance to ≥3 of the following: cefepime, piperacillin-tazobactam, meropenem, amikacin or gentamicin, and ciprofloxacin (20, 37). In general, the nominal regression analysis showed that Gram-negative bacilli were more likely to be MDR when the specimens were obtained from men ($P = 0.008$) and inpatients ($P < 0.001$). The MDR phenotype was most common in *P. aeruginosa* at 5.9%. An MDR phenotype occurred in 1.2% of *E. coli*, 0.9% of *K. pneumoniae*, 0% of *E. cloacae*, and 0% *H. influenzae* (Table 7). No statistically significant association could be made between rates of MDR *E. coli* or *P. aeruginosa* and hospital locations or specimen sources.

DISCUSSION

The CANWARD study is the first national, prospective surveillance study assessing antimicrobial resistance in hospitals across Canada. In 2008, this national surveillance study involved 10 medical centers in major population centers in 7 of the 10 provinces in Canada. Each medical center collected clinically significant bacterial isolates from blood, respiratory, wound, and urinary specimens. Previous surveillance studies had documented that more than half of all bacterial isolates recovered from clinical specimens in hospitals were from the respiratory tract (7). Such conclusions cannot be drawn from the CANWARD 2008 study, because it was designed to collect isolates from a variety of specimen sources to assess antimicrobial resistance patterns, rather than assessing the prevalence of infectious diseases in Canadian hospitals. Christensen et al. recently reported that in the United States from 1998 to 2006, respiratory tract infections were the most common infectious diseases requiring hospitalization, followed by infections of the urinary tract, cellulitis, septicemia, and abdominal/rectal infections (7). Thus, the CANWARD 2008 study, which focused on bacterial isolates obtained from blood, the respiratory tract, the urinary tract, and wounds, is reflective of the most common infectious sites in hospitals. We report that the 10 most common isolates recovered from 78.8% of all clinical specimens in hospitals across Canada were *E. coli*, MSSA, *S.*

TABLE 6. Resistance rates for the most common Gram-negative bacilli isolated from CaNAdian hospitals, based on hospital location[a]

Organism and location (*n*)	% I/% R														
	A/C	CFZ	CPM	CTR	FOX	ETP	MER	PTZ	AMK	GEN	CIP	LEV	MXF	COL	FD[b]	SXT	TGC
E.coli																	
All (1,132)	1.4/0.5	2.2/10.0	1.1/1.6	0.9/4.4	3.6/5.6	0/0	0/0	1.9/1.2	0.2/0.3	0.3/9.7	0.2/22.1	0.5/21.6	–	–	1.9/1.1	0/27.7	0.2/0
Clinic (159)	2.5/0	1.9/6.9	0.6/0.6	0/2.5	3.1/5.0	0/0	0/0	1.9/0.6	0/0	0.6/8.2	0/19.5	1.3/18.2	–	–	1.3/1.3	0/25.8	0/0
ER (453)	0.7/0.7	2.2/8.4	1.6/1.3	0.7/4.0	2.4/4.0	0/0	0/0	1.6/0.2	0.2/0.2	0/9.1	0.2/18.5	0.4/18.3	–	–	2.0/0.4	0/27.1	0.2/0
ICU (75)	5.3/0	4.0/20.0	1.3/2.7	4.0/8.0	2.7/10.7	0/0	0/0	2.7/4.0	0/0	1.3/13.3	0/28.0	1.3/26.7	–	–	2.7/1.3	0/28.0	0/0
Medical (375)	1.3/0.8	1.6/12.0	1.1/2.1	0.8/5.3	4.8/6.9	0/0	0/0	2.4/2.4	0.3/0.5	0.5/10.4	0.3/25.3	0.3/25.1	–	–	1.6/1.6	0/30.1	0.3/0
Surgical (70)	0/0	4.3/5.7	0/1.4	1.4/2.9	7.1/5.7	0/0	0/0	1.4/0	0/1.4	0/10.0	0/27.1	0/27.1	–	–	4.3/1.4	0/22.9	0/0
P. aeruginosa																	
All (373)	–	–	12.1/7.2	45.8/32.7	–	–	4.0/5.6	0/8.0	2.7/3.5	16.6/12.3	5.6/19.0	11.3/24.1	–	7.2/0.8	–	–	–
Clinic (88)	–	–	7.9/11.4	43.2/27.3	–	–	5.7/1.1	0/10.2	4.5/9.1	14.8/25.0	7.9/17.0	12.5/20.4	–	6.8/2.3	–	–	–
ER (54)	–	–	13.0/1.8	61.1/22.2	–	–	1.8/3.7	0/1.8	3.7/0	20.4/7.4	3.7/16.7	7.4/18.5	–	3.7/0	–	–	–
ICU (67)	–	–	13.4/6.0	44.8/35.8	–	–	6.0/9.0	0/7.5	3.0/6.0	14.9/10.4	4.5/19.4	13.4/25.4	–	13.4/0	–	–	–
Medical (131)	–	–	15.3/6.1	44.3/38.2	–	–	2.3/5.3	0/9.9	1.5/0.8	16.8/6.1	6.9/19.1	11.4/25.9	–	6.9/0.8	–	–	–
Surgical (33)	–	–	NA	NA	–	–	NA	NA	NA	NA	NA	NA	–	NA	–	–	–
K. pneumoniae																	
All (316)	2.8/0	4.8/6.3	0.3/0.9	1.6/1.3	4.1/3.5	0/0	0/0	1.9/2.5	0/0.6	0.6/2.8	2.2/7.3	1.3/5.1	–	–	31.3/32.6	0/11.4	3.8/0.6
Clinic (28)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA
ER (80)	0/0	1.2/1.2	0/0	1.2/0	2.5/1.2	0/0	0/0	0/1.2	0/0	0/1.2	2.5/2.5	0/0	–	–	41.2/25.0	0/8.7	0/0
ICU (63)	9.5/0	6.3/9.5	0/1.6	3.2/1.6	0/4.8	0/0	0/0	0/6.3	0/1.6	0/3.2	0/3.2	0/3.2	–	–	25.4/25.4	0/6.3	3.2/0
Medical (115)	1.7/0	7.8/8.7	0.9/1.7	0.9/2.6	5.2/4.3	0/0	0/0	4.3/2.6	0/0.9	0.9/4.3	1.7/10.4	1.7/7.8	–	–	29.6/37.4	0/15.6	6.1/0
Surgical (30)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	–	–	NA	NA	NA

[a] I, intermediate; R, resistant; NA, no isolates met criteria or there were insufficient numbers for analysis ($n < 40$); –, no defined breakpoints; A/C, amoxicillin-clavulanate; CFZ, cefazolin; CPM, cefepime; CTR, ceftriaxone; FOX, cefoxitin; ETP, ertapenem; MER, meropenem; PTZ, piperacillin-tazobactam; AMK, amikacin; GEN, gentamicin; CIP, ciprofloxacin; LEV, levofloxacin; MXF, moxifloxacin; COL, colistin; FD, nitrofurantoin; TGC, tigecycline.

[b] Indicated for use against urinary tract isolates only (CLSI M100-S19).

TABLE 7. MDR phenotypes in Canadian hospitals[a]

Organism	No. of MDR isolates/total no. of isolates	% of isolates that were MDR
E. coli	14/1,132	1.2
P. aeruginosa	22/373	5.9
K. pneumoniae	3/316	0.9
E. cloacae	0/114	0
H. influenzae	0/214	0

[a] Multidrug resistance for Gram-negative bacilli was defined as resistance to ≥3 of the following: cefepime, piperacillin-tazobactam, meropenem, amikacin or gentamicin, and ciprofloxacin.

pneumoniae, *P. aeruginosa*, *K. pneumoniae*, coagulase-negative staphylococci/*S. epidermidis*, MRSA, *H. influenzae*, *Enterococcus* spp., and *E. cloacae* (Table 1). Our data concur with previous reports that Gram-positive cocci, including MSSA, *S. pneumoniae*, MRSA, and *Enterococcus* spp., are the most common Gram-positive isolates recovered from clinical specimens in North American hospitals (13, 37). In addition, our data support that *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *E. cloacae* are the most common Gram-negative bacilli causing infections in North American hospitals (20, 37).

In CANWARD 2008, MSSA and MRSA (in all regions studied) were important isolates recovered from clinical specimens, including bacteremia, the respiratory tract, and wounds. Twenty-seven percent of all *S. aureus* isolates were MRSA (geographic variability, 19.3 to 31.6%), which is not different from the 26.0% we reported from CANWARD 2007 (39). Surprisingly, 27.6% of all MRSA isolates in Canadian hospitals were CA-MRSA, as determined genotypically. In CANWARD 2007, we reported the rate of CA-MRSA in Canadian hospitals to be 19.5%, while in a similar study assessing antimicrobial resistance in Canadian ICUs that was conducted in 2005–2006, we reported that 9.1% of all MRSA were CA-MRSA (24, 38, 39). Thus, it is clear that CA-MRSA genotypes are rapidly spreading beyond the community setting and throughout Canadian hospitals (14). CMRSA-10/USA300 continues to be the predominant CA-MRSA genotype in Canadian hospitals, as previously reported (37–39). The most common HA-MRSA genotypes in Canadian hospitals were CMRSA-2/USA100/800 (81.9%) and CMRSA-6 or CMRSA-3 (12.8%), as has also been previously documented (8, 23, 37). The resistance rates among MRSA were high (>50%) with fluoroquinolones and macrolides (such as clarithromycin), as well as clindamycin, but lower with SXT (10.3%). These resistance rates are consistent with previous reports (23, 37) and suggest that SXT remains a reasonable empirical treatment for mild to moderate infections (e.g., skin and soft tissue infections) caused by CA-MRSA or HA-MRSA. Eight of 272 (2.9%) MRSA isolates demonstrated vancomycin MICs of 2 μg/ml, which is an increase from CANWARD 2007, for which we documented a rate of 1.0% (38, 39). Although we did not assess the prevalence of hetero-resistant vancomycin-intermediate *S. aureus* (hVISA), a recent Canadian study reported that 8.1% (22 of 271) of MRSA isolates with a vancomycin MIC of 2 μg/ml collected across Canada from 1995 to 2006 were hVISA based on population analysis profiling (1). Similarly, a recent analysis

from Detroit identified 8.3% (of 917 strains assessed from 2003 to 2007) of MRSA isolates as hVISA (31).

We report that only 3.1% of all enterococci were VRE in our study, of which all were *E. faecium* and displayed the *vanA* genotype. In CANWARD 2007, we reported 1.8% VRE with the majority (62.5%) having the *vanA* genotype (39). This study confirms that *E. faecium* carrying *vanA* continues to be the predominant VRE genotype in North America (12, 36, 38). The low level of VRE across Canada has been previously documented and highlights the lack of spread of VRE across the country (36, 38). The continued low level of VRE in Canadian hospitals likely reflects the use of active surveillance programs as well as infection control programs (e.g., aggressive hand hygiene) and antimicrobial stewardship programs, which have been shown to prevent VRE and MRSA infections (11, 16, 18, 32). None of the enterococci displayed resistance to tigecycline or daptomycin.

The CANWARD 2008 study found that 4.9% of *E. coli* isolates were ESBL producers (an increase from 3.4% in CANWARD 2007) and that all areas of the hospital were affected. The observations that ESBL-producing *E. coli* were identified in all geographic regions of the country and 76.4% of the isolates displayed an MDR phenotype alert researchers and clinicians that MDR ESBL-producing *E. coli* isolates are increasing in Canadian hospitals. This study demonstrated that the CTX-M genotype ($bla_{\text{CTX-M-15}}$ and $bla_{\text{CTX-M-14}}$) was the predominant genotype in Canadian hospitals. Other studies assessing ESBL-producing *E. coli* have shown that the CTX-M genotype is spreading rapidly in both community and hospital settings (3, 5, 19, 22, 26–28). Recently, Peirano et al. reported on ESBL-producing *E. coli* from 11 Canadian medical units based on phenotypic and genotypic methods to characterize the isolates. CTX-M-15 was the predominant genotype produced (71%; 148/209), while 8% (17/209) produced CTX-M-14 (26). ESBL-producing *E. coli* most commonly belonged to clonal complex ST131 (46%; 96/209) (26). CANWARD 2008 highlights the rapid spread of CTX-M-15 *E. coli* and MDR CTX-M-15 in Canadian hospitals. This MDR phenotype may be spreading rapidly in part due to the continued extensive use of broad-spectrum cephalosporins and fluoroquinolones. Hsu et al. recently reported a correlation between the use of broad-spectrum cephalosporins and fluoroquinolones and antimicrobial-resistant *E. coli* (17).

This study found associations between increasing age and inpatient status and resistance in Gram-positive cocci. For Gram-negative bacilli, resistance was more likely to occur in isolates obtained from inpatients and men. These data support the current literature, which indicates that antimicrobial resistance generally increases with increasing age and among inpatients (4, 34). Especially among urinary tract isolates of *E. coli*, it has been established that resistance is higher in men than in women and increases with age (4). With *E. coli* and *P. aeruginosa* (excluding the cystic fibrosis clinics), antimicrobial resistance rates were highest in isolates obtained from the ICU. This finding is consistent with previous studies where higher resistance rates in the ICU were reported for Gram-negative bacilli (20, 29, 37).

The lowest rates of resistance for Gram-negative bacilli occurred with amikacin, amoxicillin-clavulanate, cefepime, doripenem, ertapenem (except *P. aeruginosa*), meropenem, and piperacillin-tazobactam, which is consistent with previous reports (20, 29, 37). With *P. aeruginosa*, carbapenem activity was observed in the following order: doripenem > meropenem (imipenem was not tested). The low level of resistance in Gram-negative bacilli with amikacin likely reflects the low usage of aminoglycosides in favor of the fluoroquinolones in Canada and the United States over the past decade. In contrast, fluoroquinolone resistance was high with *E. coli* (21.6 to 22.1%) and *P. aeruginosa* (19.0 to 24.1%), which is consistent with other reports (20, 29, 37) and reflects extensive fluoroquinolone usage (17). A recent report documented increasing prevalence of MDR Gram-negative bacilli in ICUs in the United States (20). Our definition of multidrug resistance for Gram-negative bacilli (resistance to ≥3 of the following: cefepime, piperacillin-tazobactam, meropenem, amikacin or gentamicin, and ciprofloxacin) was slightly more restrictive than that used in the U.S. study; thus, it was not surprising that our MDR rate of 5.9% with *P. aeruginosa* was somewhat lower than that previously reported in the United States of 9.3% (20). MDR rates in Gram-negative bacilli in Canadian hospitals (*E. coli*, 1.2%; *E. cloacae*, 0%; *K. pneumoniae*, 0.9%) are lower than those in U.S. institutions (*E. coli*, 2.0%; *E. cloacae*, 5.9%; *K. pneumoniae*, 13.3%) (20). The explanation for the lower MDR rates with *Enterobacteriaceae* (*E. coli*, *E. cloacae*, and *K. pneumoniae*) in Canada is unclear but may include the fact that Canada has a lower prevalence of ESBL-producing *Enterobacteriaceae* or the fact that Canada aggressively promotes active surveillance programs, infection control programs (e.g., diligent hand hygiene), and antimicrobial stewardship programs (2, 3, 5, 11, 16, 18, 32). MDR ESBL-producing *E. coli* isolates were all susceptible to the carbapenems doripenem, ertapenem, and meropenem, as well as to tigecycline.

The limitations of the CANWARD study include the fact that we cannot be certain that all clinical specimens represent active infection. As in our previous CANWARD 2007 and CAN-ICU studies (37–39), we asked centers to provide potentially pathogenic isolates from "clinically significant" specimens from patients with a presumed or proven infectious disease. Although it is possible that not all of the organisms were isolated from actual infections in patients, we believe that the vast majority of the isolates would have been collected from clinically significant samples, as we excluded all surveillance swabs, duplicate swabs, eye, ear, nose, and throat swabs, and genital cultures. Another limitation of this study is that we did not have admission date data for each patient/clinical specimen, and thus we were not able to provide a completely accurate description of community versus nosocomial onset. The CANWARD study assessed antimicrobial resistance rates in tertiary care medical centers across Canada and thus may depict inflated resistance rates compared to smaller, community practice hospitals. In this study, CA-MRSA and HA-MRSA were defined genotypically, not epidemiologically, and it has been shown epidemiologically that CA-MRSA genotypes can be associated with HA infections and that HA-MRSA can be associated with CA infections (8). Susceptibility testing was not performed (nor fully reported) for all antimicrobial agents due to a lack of space on the susceptibility panels utilized (or in data tables). It is recognized that data on antimicrobials such as ceftazidime, imipenem, tobramycin, and others would be beneficial, as different hospital formularies stock these and

other antimicrobials not tested in this study. Finally, performing statistical analyses by collapsing various Gram-positive cocci (e.g., MSSA, MRSA, and VRE) or various Gram-negative bacilli (e.g., *Enterobacteriaceae* and nonfermenters) together to assess risk factors for resistance may not be appropriate. The analysis was performed to assess general risk factor trends.

In conclusion, *E. coli*, *S. aureus* (MSSA and MRSA), *P. aeruginosa*, *S. pneumoniae*, *K. pneumoniae*, *H. influenzae*, and *Enterococcus* spp. are the most common isolates recovered from clinical specimens in Canadian hospitals. The prevalence of MRSA was 27.0% (of which, genotypically, 27.6% was CA-MRSA), the prevalence of VRE was 3.1%, and ESBL-producing *E. coli* occurred in 4.9% of isolates. An MDR phenotype is common with *P. aeruginosa* in Canadian hospitals.

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